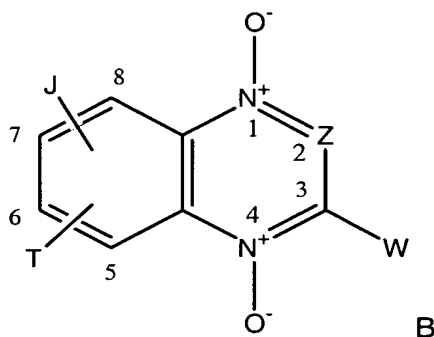
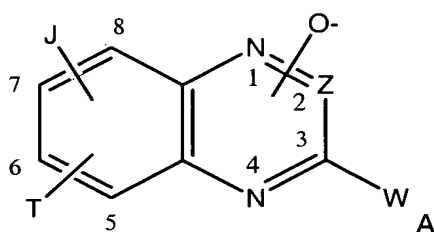


Claims

- 1 A cytotoxic synergistic composition, comprising an effective amount of a
 5 benzoazine N-mono oxide compound of Formula A or a pharmacologically acceptable salt thereof and an effective amount of a benzoazine 1,4 dioxide compound of Formula B or a pharmacologically acceptable salt thereof



wherein in Formulae A or B
 Z is N or C-CN, and

- 15 wherein in Formula A when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

- wherein J in Formulae A or B represents at one or more of the available carbons 5-8 on
 20 the benzo ring the following groups:

halo, H, R, OH, OR, NO₂, NH₂, NHR, NR₂, SH, SR, SO₂R, CF₃, CN, CO₂H, CO₂R, CHO, COR, CONH₂, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

- wherein each R is independently selected from an optionally substituted
 25 C₁₋₆ alicyclic or an optionally substituted C₃₋₆ cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR¹, NO₂, NH₂,

NHR^1 , NR^1R^1 , SH , SR^1 , imidazolyl, R^1 -piperazinyl, morpholino, SO_2R^1 , CF_3 , CN , CO_2H , CO_2R^1 , CHO , COR^1 , CONH_2 , CONHR^1 , CONR^1R^1 ;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1 , NH_2 , NHR^1 , NR^1R^1 , SH , SR^1 , imidazolyl, R^1 -piperazinyl, morpholino, SO_2R^1 , CF_3 , CN , CO_2H , CO_2R^1 , CHO , COR^1 , CONH_2 , CONHR^1 , CONR^1R^1 , and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted

C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2 , NHR^2 , NR^2_2 or N(OH)R^2 wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN , CO_2H or SH , and

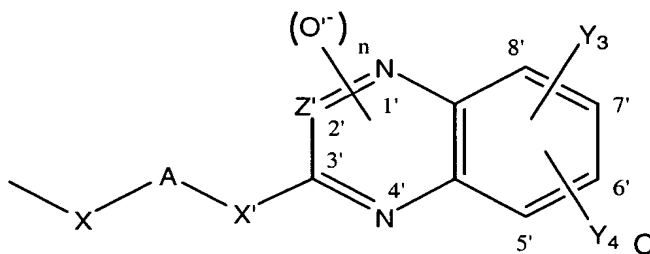
wherein W in Formulae A or B can represent $-\text{X}-\text{A}$, wherein $-\text{X}-\text{A}$ together can represent H, or halogen; or

X represents O, S, NH, NMe, CH_2 , SO, SO_2 , CONH, NHCO, CO or CO_2 , and

A represents H, an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR^3 , NH_2 , NHR^3 , NR^3_2 , or

N(OH)R^3 wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN , CO_2H or SH ; and wherein the optionally substituted C_{1-12} alkyl chain can optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR^4 , CONH, CONR^4 , NHCO, NR^4CO , where each R^4 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional R^4 substituents are each independently selected from OH, OR, NH_2 , NHR^5 , NR^5_2 or N(OH)R^5 wherein each R^5 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN , CO_2H or SH , or a pharmacologically acceptable salt thereof, or

W can represent a group of Formula C



wherein in a group of Formula C

n represents either 1 or 2,

Z' is selected from N or C-CN, and when Z' represents N, and n represents 1 the N-oxide moiety occupies one of the 1'-, 2'-, or 4'-positions and when Z' represents C-

5 CN, the N-oxide moiety occupies one of the 1'-, or 4'-positions; and when Z' represents N or C-CN, and n represents 2 the N-oxide moieties occupy the 1' and 4'-positions

Y₃ and Y₄ each represent at one or more of the available carbons 5'-8' on the benzo ring the following groups:

10 halo, H, R, OH, OR, NO₂, NH₂, NHR, NR₂, SH, SR, SO₂R, CF₃, CN, CO₂H, CO₂R, CHO, COR, CONH₂, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R is independently selected from an optionally substituted

15 C₁₋₆ alicyclic or an optionally substituted C₃₋₆ cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR¹, NO₂, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR¹, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R¹ is independently selected from an optionally substituted

25 C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH₂, NHR², NR²₂ or N(OH)R² wherein each R² is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, and

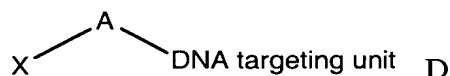
30 X' represents O, NH, NMe, or CH₂,

A represents an optionally substituted C₁₋₁₂ alkyl group wherein the optional substituents are each independently selected from OH, OR³, NH₂, NHR³, NR³₂, or N(OH)R³ wherein each R³ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and wherein the optionally substituted C₁₋₁₂ alkyl chain is optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR⁴, CONH, CONR⁴, NHCO, NR⁴CO, where each R⁴ is independently selected from an optionally substituted C₁₋₄ alkyl or an

optionally substituted C₂₋₄ alkenyl group and wherein the optional R⁴ substituents are each independently selected from OH, OR, NH₂, NHR⁵, NR⁵₂ or N(OH)R⁵ wherein each R⁵ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, or

5

W can represent a group of Formula D



10 wherein X represents NH, NMe, CH₂, or O;

A represents an optionally substituted C₁₋₁₂ alkyl group wherein the optional substituents are each independently selected from OH, OR, NH₂, NHR³, NR³₂, or N(OH)R³ wherein each R³ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and wherein the optionally substituted C₁₋₁₂ alkyl

15 chain is optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR⁴, CONH, CONR⁴, NHCO, NR⁴CO, where each R⁴ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional R⁴ substituents are each independently selected from OH, OR, NH₂, NHR⁵, NR⁵₂ or N(OH)R⁵ wherein
20 each R⁵ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random sequence DNA of >10³ M⁻¹ at an ionic strength of 0.01 M at 20 °C,

25

wherein T in Formulae A or B, represent at one of carbons 5-8 on the benzo ring the following groups:

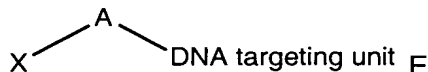
halo, H, R, OH, OR, NO₂, NH₂, NHR, NR₂, SH, SR, SO₂R, CF₃, CN, CO₂H, CO₂R, CHO, COR, CONH₂, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl,
30 morpholino;

wherein each R is independently selected from an optionally substituted C₁₋₆ alicyclic or an optionally substituted C₃₋₆ cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR¹, NO₂, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹;
35

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR¹, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹,
 5 CONH₂, CONHR¹, CONR¹R¹, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R¹ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH₂, NHR², NR²₂ or
 10 N(OH)R² wherein each R² is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, or

T represents a group of Formula E



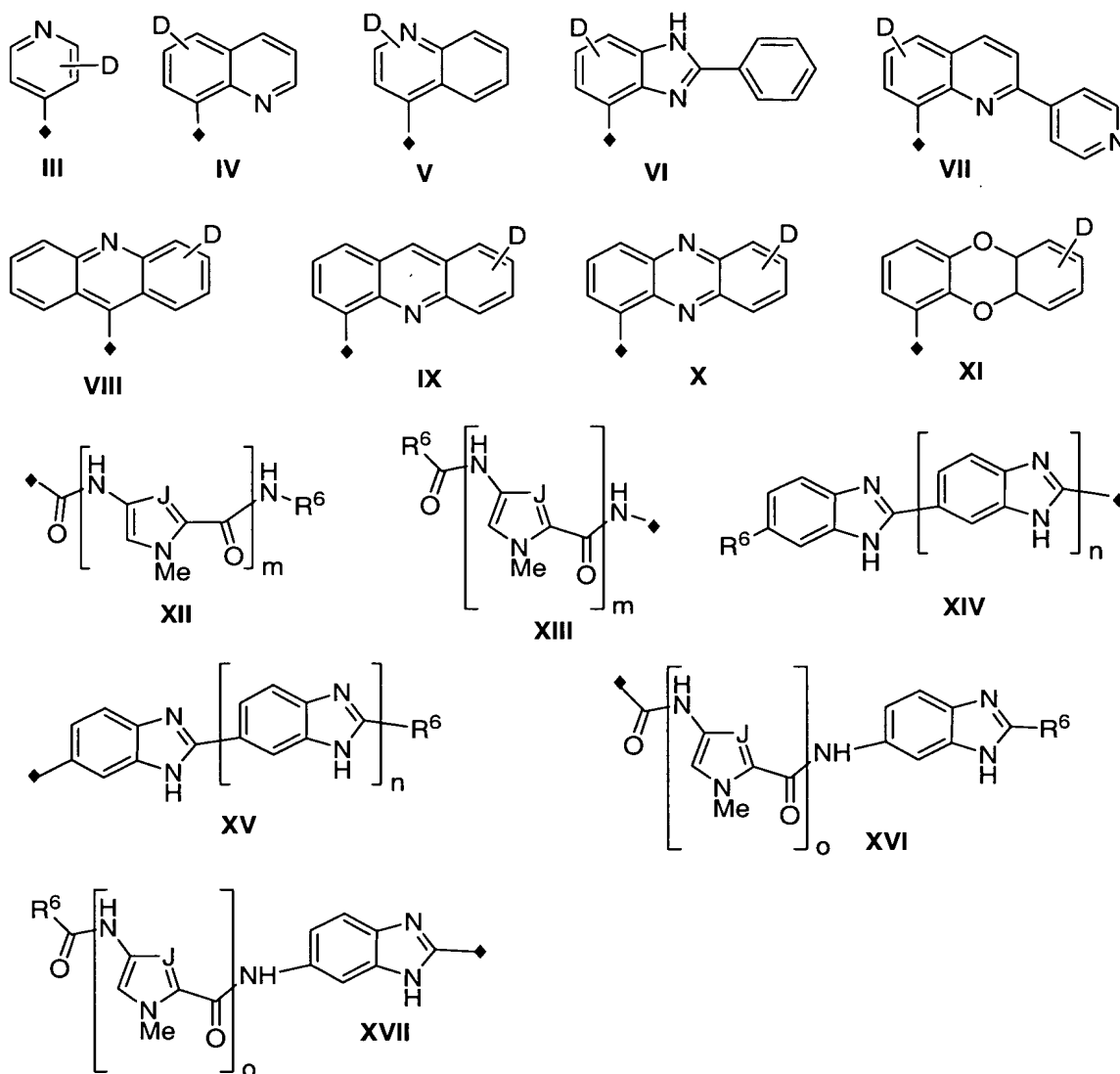
15

wherein X represents O, S, NH, NMe, CH₂, SO, SO₂, CONH, NHCO, CO, CO₂, or O and

A represents an optionally substituted C₁₋₁₂ alkyl group wherein the optional substituents are each independently selected from OH, OR, NH₂, NHR³, NR³₂, or
 20 N(OH)R³ wherein each R³ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and wherein the optionally substituted C₁₋₁₂ alkyl chain is optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR⁴, CONH, CONR⁴, NHCO, NR⁴CO, where each R⁴ is independently selected from an optionally substituted C₁₋₄ alkyl or an
 25 optionally substituted C₂₋₄ alkenyl group and wherein the optional R⁴ substituents are each independently selected from OH, OR, NH₂, NHR⁵, NR⁵₂ or N(OH)R⁵ wherein each R⁵ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons
 30 that has an association constant (K) for binding to double-stranded random-sequence DNA of >10³ M⁻¹ at an ionic strength of 0.01 M at 20 °C.

2 A composition according to claim 1 wherein the DNA targeting agent defined in claim 1 for a group of Formula D or Formula E is independently selected from any one
 35 of the formulae III- XVII,



wherein in structures **XII-XVII** R^6 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 , NO_2 , NH_2 , NHR^7 , NR^7R^7 , SR^7 , imidazolyl, R^7 -piperazinyl, morpholino, SO_2R^7 , CF_3 , CN, CO_2H , CO_2R^7 , CHO, COR^7 , $CONH_2$, $CONHR^7$, $CONR^7R^7$;

R^6 can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 , NH_2 , NHR^7 , NR^7R^7 , SH, SR^7 , imidazolyl, R^7 -piperazinyl, morpholino, SO_2R^7 , CF_3 , CN, CO_2H , CO_2R^7 , CHO, COR^7 , $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

- wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8 , NH_2 , NHR^8 , NR^8_2 or $N(OH)R^8$ wherein each R^8 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN , CO_2H or SH ;
- D represents up to four of the following groups as substituents at any available ring carbon position; H, R^9 , hydroxy, alkoxy, halogen, NO_2 , NH_2 , NHR^9 , NR^9_2 , SH , SR^9 , SO_2R^9 , CF_3 , CN , CO_2H , CO_2R^9 , CHO , COR^9 , $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, wherein each R^9 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10} , NH_2 , NHR^{10} , NR^{10}_2 or $N(OH)R^{10}$ wherein each R^{10} is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN , CO_2H or SH ;
- and wherein any available ring carbon position of formulae **III** - **XVII** can also be optionally replaced by $-N-$ when the valency and configuration of the formula allows, the point of attachment of formulae **III**- **XVII** to the A group defined above is represented by \blacklozenge ; and
- wherein in formulae **XII**, **XIII**, m is selected from 2, 3 or 4, and
- wherein in formulae **XII**, **XIII**, **XVI** and **XVII**, J is selected from CH or N;
- and wherein in formulae **XIV** and **XV** n is selected from 0, 1 or 2;
- and wherein in formulae **XVI** and **XVII** o is selected from 1 and 2.
- 3 A composition according to claim 2 wherein the DNA targeting unit of Formula D
25 or Formula E is selected from one of formulae **V**, **VI**, **VII**, **VIII**, **IX** or **X**.
- 4 A composition according to claim 2 wherein substituent D of the DNA targeting
unit of Formulae **III** - **XI** is H or Me.
- 30 5 A composition according to claim 1 wherein W in the compound of Formula A as
defined in claim 1 represents a $NH(C_0-C_{12})$ optionally substituted alkyl or a $O(C_0-C_{12})$
optionally substituted alkyl.
- 6 A composition according to claim 5 wherein W represents NH_2 ,
35 $NHCH_2CH_2NHCH_3$, $NHCH_2CH_2N(CH_3)_2$ or OCH_3 .

7 A method of treating a subject in need of cancer therapy, said method comprising the steps of administering to said subject a cytotoxic effective amount of a composition including an effective amount of one or more compounds of Formula A and one or more compounds of formula B as defined in claim 1 or claim 2 to the tumour cells
5 in said subject.

8 The method according to claim 7 wherein the steps of administration of a compound of Formula A and B are simultaneous or sequential.

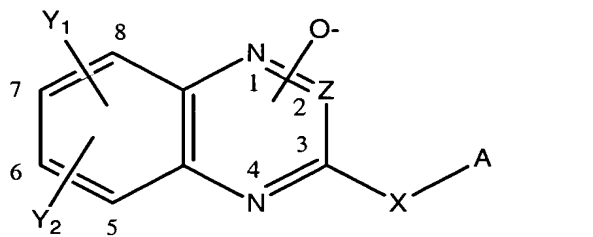
10 9 The method according to claim 7 wherein the tumour cells are in a hypoxic environment.

10 The method according to claim 7 including the further step of administering the composition as defined in claim 7 in combination with one or more other
15 chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancer therapy required.

11 The method according to claim 10 wherein radiotherapy is administered to the tumour cells before, during or after the administration of the composition.

20 12 The method according to claim 10 wherein the chemotherapeutic agents are selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide or other DNA alkylating agents, doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors,
25 methotrexate, gemcitabine or other antimetabolites.

13 A compound of Formula I,



wherein

30 Z is selected from N or C-CN, and when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

Y₁ and Y₂ each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO₂, NH₂, NHR, NR₂, SH, SR, SO₂R, CF₃, CN, CO₂H, CO₂R, CHO, COR, CONH₂, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R is independently selected from an optionally substituted C₁₋₆ alicyclic or an optionally substituted C₃₋₆ cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR¹, NO₂, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR¹, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R¹ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH₂, NHR², NR²₂ or N(OH)R² wherein each R² is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, and

wherein A and X together represent H, or halogen; or

X represents O, S, NH, NMe or CH₂ and

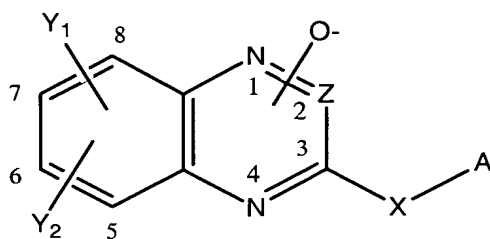
A represents H, an optionally substituted C₁₋₁₂ alkyl group wherein the optional substituents are each independently selected from OH, OR³, NH₂, NHR³, NR³₂, or N(OH)R³ wherein each R³ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and wherein the optionally substituted C₁₋₁₂ alkyl chain can be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR⁴, CONH, CONR⁴, NHCO, NR⁴CO, where each R⁴ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional R⁴ substituents are each independently selected from OH, OR, NH₂, NHR⁵, NR⁵₂ or N(OH)R⁵ wherein each R⁵ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, or a pharmacologically acceptable salt thereof,

with the proviso that the following compounds are excluded

3-Amino-1,2,4-benzotriazine-1-oxide,

- 3-Amino-7-trifluoromethyl-1,2,4-benzotriazine-1-oxide,
 3-Amino-7-carbamyl-1,2,4-benzotriazine-1-oxide,
 3-Amino-7-chloro-1,2,4-benzotriazine-1-oxide,
 3-Amino-7-nitro-1,2,4-benzotriazine-1-oxide
 5 3-Chloro-1,2,4-benzotriazine-1-oxide,
 3-(3-N,N-Diethylaminopropylamino)- 3-amino-1,2,4-benzotriazine-1-oxide,
 3-Chloro-7-nitro-1,2,4-benzotriazine-1-oxide,
 7-Nitro-(3-(2-N,N-diethylamino-ethylamino)-1,2,4-benzotriazine-1-oxide,
 8-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide,
 10 8-Methyl-1,2,4-benzotriazin-3-amine 1-oxide,
 8-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide,
 8-Chloro-1,2,4-benzotriazin-3-amine 1-oxide,
 8-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide,
 8-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,
 15 8-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,
 3-Amino-1,2,4-benzotriazin-7-ol 1-oxide,
 3-Amino-1,2,4-benzotriazin-7-ol 1-oxide,
 7-Methyl-1,2,4-benzotriazin-3-amine 1-oxide,
 7-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide,
 20 7-Chloro-1,2,4-benzotriazin-3-amine 1-oxide,
 7-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide,
 7-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,
 7-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,
 7-Nitro-1,2,4-benzotriazin-3-amine 1-oxide,
 25 6-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide,
 6-Methyl-1,2,4-benzotriazin-3-amine 1-oxide,
 6-Phenyl-1,2,4-benzotriazin-3-amine 1-oxide,
 6-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide,
 6-Chloro-1,2,4-benzotriazin-3-amine 1-oxide,
 30 6-Trifluoromethyl-1,2,4-benzotriazin-3-amine 1-oxide,
 6-(Methylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,
 6-(Butylsulfanyl)-1,2,4-benzotriazin-3-amine 1-oxide,
 5-Methoxy-1,2,4-benzotriazin-3-amine 1-oxide,
 5-Methyl-1,2,4-benzotriazin-3-amine 1-oxide,
 35 5-Chloro-1,2,4-benzotriazin-3-amine 1-oxide,
 5-Fluoro-1,2,4-benzotriazin-3-amine 1-oxide,
 N⁷,N⁷-Dimethyl-1,2,4-benzotriazine-3,7-diamine 1-oxide,

- 3-Chloro-1,2,4-benzotriazine 1-oxide,
 3-Methyl-1,2,4-benzotriazine 1-oxide,
 3-Ethyl-1,2,4-benzotriazine 1-oxide,
 3-Phenyl-1,2,4-benzotriazine 1-oxide,
 5 3-(4-Methoxyphenyl)-1,2,4-benzotriazine 1-oxide,
 3-Vinyl-1,2,4-benzotriazine 1-oxide,
 3-Allyl-1,2,4-benzotriazine 1-oxide,
 3-(2-Hydroxyethyl)-1,2,4-benzotriazine 1-oxide,
 3-(2-Methoxyethyl)-1,2,4-benzotriazine 1-oxide,
 10 *N*-Phenyl-1,2,4-benzotriazin-3-amine 1-oxide,
 3-Methoxy-1,2,4-benzotriazine 1-oxide,
 3-Chloro-7-methyl-1,2,4-benzotriazine 1-oxide,
 3-Chloro-7-methoxy-1,2,4-benzotriazine 1-oxide,
 1,2,4-benzotriazine 1-oxide,
 15 1,2,4-benzotriazin-3-amine 2-oxide, and
 1,2,4-benzotriazin-3-amine 4-oxide.
- 14 The compound of Formula I according to claim 13 wherein Z is N.
- 20 15 The compound of Formula I according to claim 13 wherein X is NH or CH₂.
- 16 The compound of Formula I according to claim 13 wherein
 –X-A represents a NH(C₀–C₁₂) optionally substituted alkyl or an O(C₀–C₁₂) optionally
 substituted alkyl, such as NHCH₂CH₂NHCH₃, NHCH₂CH₂N(CH₃)₂ or OCH₃.
- 25 17 The compound of Formula I according to claim 13 wherein Y₁ and Y₂ each
 represent H.
- 18 The compound of Formula I according to claim 13 in which the N-oxide moiety
 30 occupies the 1-position.
- 19 A method of treating a subject in need of cancer therapy, said method
 comprising the steps of administering to said subject a cytotoxic effective amount of a
 compound of Formula I
- 35



wherein

Z is selected from N or C-CN, and when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

Y_1 and Y_2 each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO_2 , NH_2 , NHR, NR_2 , SH, SR, SO_2R , CF_3 , CN, CO_2H , CO_2R , CHO, COR, CONH_2 , CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R can be independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR^1 , NO_2 , NH_2 , NHR^1 , NR^1R^1 , SH, SR^1 , imidazolyl, R^1 -piperazinyl, morpholino, SO_2R^1 , CF_3 , CN, CO_2H , CO_2R^1 , CHO, COR^1 , CONH_2 , CONHR¹, CONR^1R^1 ;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^1 , NH_2 , NHR^1 , NR^1R^1 , SH, SR^1 , imidazolyl, R^1 -piperazinyl, morpholino, SO_2R^1 , CF_3 , CN, CO_2H , CO_2R^1 , CHO, COR^1 , CONH_2 , CONHR¹, CONR^1R^1 , and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^1 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH_2 , NHR^2 , NR^2_2 or $\text{N}(\text{OH})\text{R}^2$ wherein each R^2 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN, CO_2H or SH, and

wherein A and X together represent H, or halogen; or

X represents O, S, NH, NMe or CH_2 and

A represents H, an optionally substituted C_{1-12} alkyl group wherein the optional substituents are each independently selected from OH, OR, NH_2 , NHR^3 , NR^3_2 , or $\text{N}(\text{OH})\text{R}^3$ wherein each R^3 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH,

NO₂, NH₂, CF₃, CN, CO₂H or SH; and wherein the optionally substituted C₁₋₁₂ alkyl chain is optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR⁴, CONH, CONR⁴, NHCO, NR⁴CO, where each R⁴ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional R⁴ substituents are each independently selected from OH, OR, NH₂, NHR⁵, NR⁵₂ or N(OH)R⁵ wherein each R⁵ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, or a pharmacologically acceptable salt thereof

to the tumour cells in said subject.

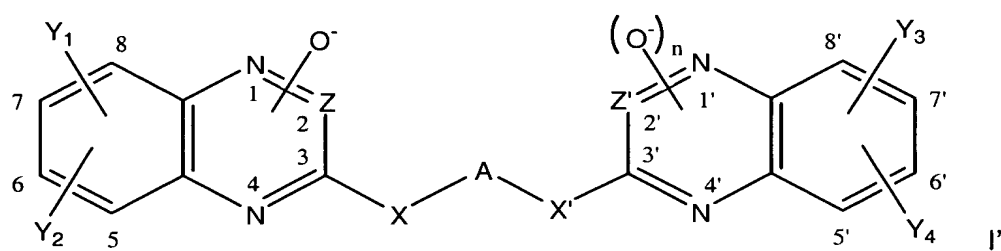
The method according to claim 19 wherein the tumour cells are in a hypoxic environment.

The method according to claim 19 further including the step of administering the compound of Formula I as defined in claim 19 in combination with one or more other chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancer therapy required.

The method according to claim 19 wherein radiotherapy is administered to the tumour cells before, during or after the administration of the compound of Formula I.

The method according to claim 21 wherein the chemotherapeutic agents are selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide or other DNA alkylating agents, doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

A compound of Formula I',



wherein

n represents either 1 or 2,

Z or Z' is selected from N or C-CN, and when Z or Z' represents N, and n represents 1 each N-oxide moiety occupies one of the 1-, 2-, or 4-positions or 1'-, 2'-, or 4'-positions respectively and when Z or Z' represents C-CN, each N-oxide moiety occupies one of the 1-, or 4-positions or 1'-, or 4'-positions respectively; and when Z' represents N, and n represents 2, the N'-oxide moieties occupy the 1'- and 4'-positions and when Z' represents C-CN, and n represents 2 the N'-oxide moieties occupy the 1'-, and 4'-positions;

Y₁, Y₂, Y₃ and Y₄ each represent at one or more of the available carbons 5-8 or one or more of the available carbons 5'-8' on the respective benzo ring the following groups:

halo, H, R, OH, OR, NO₂, NH₂, NHR, NR₂, SH, SR, SO₂R, CF₃, CN, CO₂H, CO₂R, CHO, COR, CONH₂, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

wherein each R is independently selected from an optionally substituted C₁₋₆ alicyclic or an optionally substituted C₃₋₆ cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR¹, NO₂, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹;

R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR¹, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R¹ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH₂, NHR², NR²₂ or N(OH)R² wherein each R² is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, and

wherein X represents NH, NMe, CH₂, or O;

A represents an optionally substituted C₁₋₁₂ alkyl group wherein the optional substituents are each independently selected from OH, OR³, NH₂, NHR³, NR³₂, or N(OH)R³ wherein each R³ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and wherein the optionally substituted C₁₋₁₂ alkyl chain is optionally

interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR⁴, CONH, CONR⁴, NHCO, NR⁴CO, where each R⁴ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional R⁴ substituents are each independently selected from OH, OR, NH₂, NHR⁵, NR⁵₂ or N(OH)R⁵ wherein each R⁵ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, or a pharmacologically acceptable salt thereof.

25 The compound of Formula I' as claimed in claim 24 in which X is NH or CH₂.

10

26 The compound of Formula I' as claimed in claim 24 in which Y₁ and Y₂ each represent H.

27 The compound of Formula I' as claimed in claim 24 in which A is –

15

(CH₂)₂NMe(CH₂)₂–

28 The compound of Formula I' as claimed in claim 24 in which the N-oxides are positioned at the 1-position and the 1'-position.

20

29 A method of treating a subject in need of cancer therapy, said method comprising the steps of administering to said subject a cytotoxic effective amount of a compound of Formula I' as defined in claim 24 to the tumour cells in said subject.

30 The method as claimed in claim 29 wherein the tumour cells are in a hypoxic environment.

25

31 The method as claimed in claim 29 which includes the further step of administering the compound of Formula I' as defined in claim 24 in combination with one or more other chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancer therapy required.

30

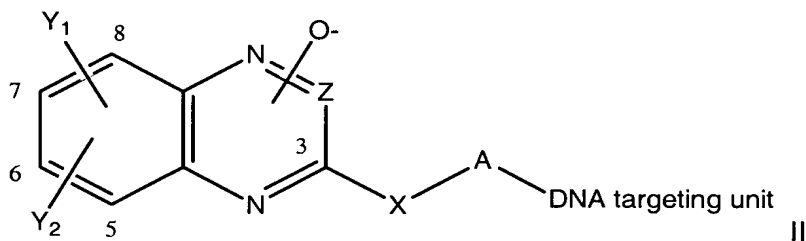
32 The method as claimed in claim 31 wherein radiotherapy is administered to the tumour cells before, during or after the administration of the compound of Formula I'.

35

33 The method as claimed in claim 31 wherein the chemotherapeutic agents are selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide or other DNA alkylating agents,

doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

34 A compound of Formula II,



wherein

Z is selected from N or C-CN, and when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

10 Y₁ and Y₂ each represent at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO₂, NH₂, NHR, NR₂, SH, SR, SO₂R, CF₃, CN, CO₂H, CO₂R, CHO, COR, CONH₂, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

15 wherein each R is independently selected from an optionally substituted C₁₋₆ alicyclic or an optionally substituted C₃₋₆ cyclic alkyl group, and wherein the said optional substituents are each independently selected from; halo, OH, OR¹, NO₂, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹;

20 R can also represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR¹, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹, and each heteroaryl group contains one or more

25 heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R¹ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional substituents are each independently selected from OH, OR, NH₂, NHR², NR²₂ or N(OH)R² wherein each R² is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, and

wherein X represents NH, NMe, CH₂, or O;

A represents an optionally substituted C₁₋₁₂ alkyl group wherein the optional substituents are each independently selected from OH, OR³, NH₂, NHR³, NR³₂, or N(OH)R³ wherein each R³ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and wherein the optionally substituted C₁₋₁₂ alkyl chain can be optionally interrupted or extended by one or more heteroatom containing linkage moieties selected from O, NH, NR⁴, CONH, CONR⁴, NHCO, NR⁴CO, where each R⁴ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional R⁴ substituents are each independently selected from OH, OR, NH₂, NHR⁵, NR⁵₂ or N(OH)R⁵ wherein each R⁵ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of $>10^3 \text{ M}^{-1}$ at an ionic strength of 0.01 M at 20 °C,

or a pharmacologically acceptable salt thereof.

35 The compound of Formula II as claimed in claim 34, wherein Z is N.

36 The compound of Formula II as claimed in claim 34 wherein X is NH or CH₂.

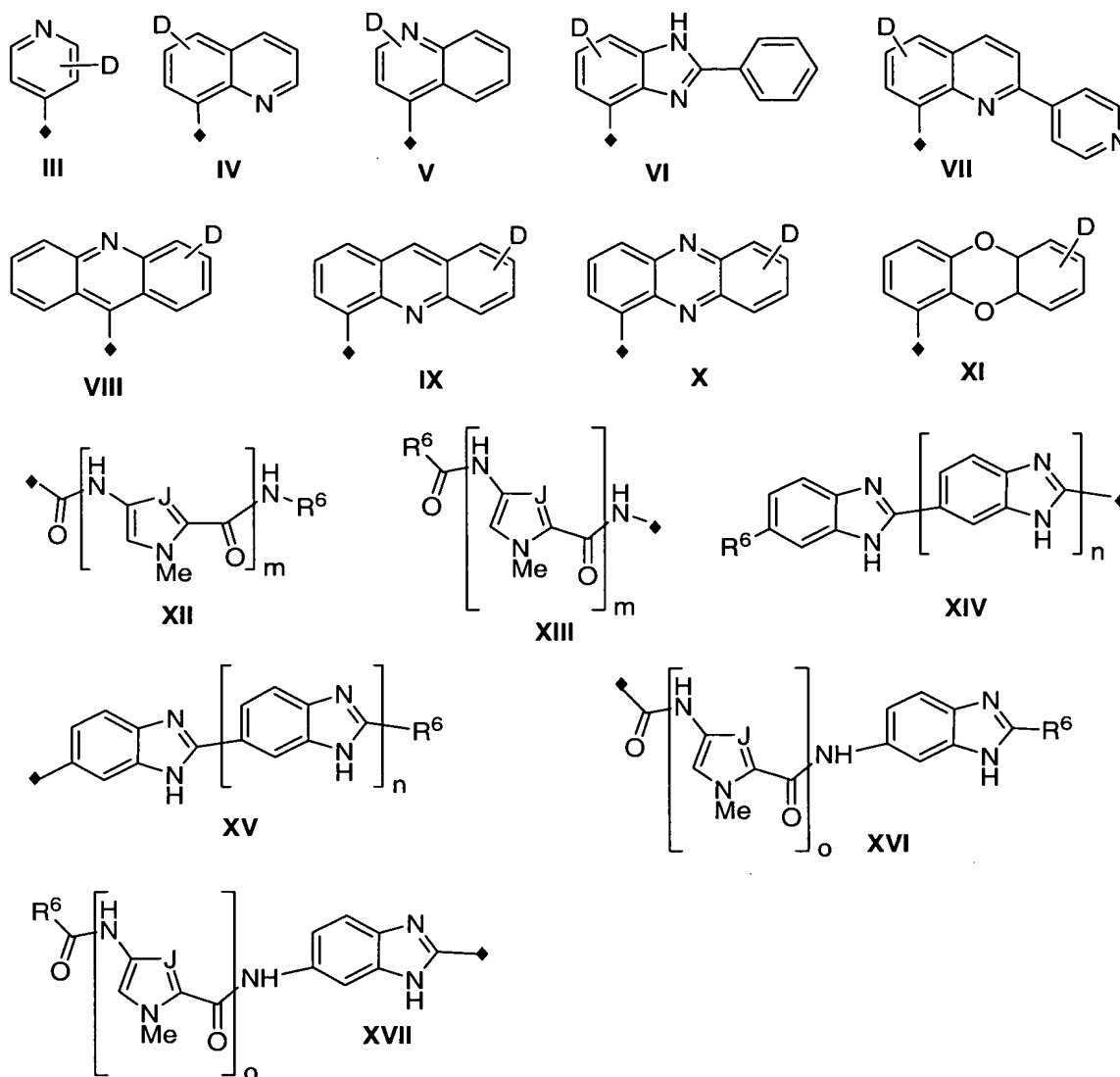
37 The compound of Formula II as claimed in claim 34 wherein the N-oxide is at the 1-position.

38 The compound of Formula II as claimed in claim 34 wherein Y₁ and Y₂ each represent H.

39 The compound of Formula II as claimed in claim 34 wherein Y₁ represents Me.

40 The compound of Formula II as claimed in claim 34 wherein A is selected from -(CH₂)₆NH-, -(CH₂)₃NH(CH₂)₃NHCO-, -(CH₂)₃NMe(CH₂)₃NHCO-, -(CH₂)₃NH-, -(CH₂)₂NH(CH₂)₂NHCO- or -(CH₂)₂NMe(CH₂)₂NHCO-.

41 The compound of Formula II as claimed in claim 34 wherein the DNA-targeting unit is selected from one of formulae III- XVII,



wherein in structures **XII-XVII** R^6 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 , NO_2 , NH_2 , NHR^7 , NR^7R^7 , SR^7 , imidazolyl, R^7 -piperazinyl, morpholino, SO_2R^7 , CF_3 , CN, CO_2H , CO_2R^7 , CHO, COR^7 , CONH_2 , CONHR^7 , CONR^7R^7 ;

R^6 can also be represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 , NH_2 , NHR^7 , NR^7R^7 , SH, SR^7 , imidazolyl, R^7 -piperazinyl, morpholino, SO_2R^7 , CF_3 , CN, CO_2H , CO_2R^7 , CHO, COR^7 , CONH_2 , CONHR^7 , CONR^7R^7 , and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8 , NH_2 , NHR^8 , NR^8_2 or $N(OH)R^8$ wherein each R^8 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN , CO_2H or SH ;

D represents up to four of the following groups as substituents at any available ring carbon position; H, R^9 , hydroxy, alkoxy, halogen, NO_2 , NH_2 , NHR^9 , NR^9_2 , SH , SR^9 , SO_2R^9 , CF_3 , CN , CO_2H , CO_2R^9 , CHO , COR^9 , $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino, wherein each R^9 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10} , NH_2 , NHR^{10} , NR^{10}_2 or $N(OH)R^{10}$ wherein each R^{10} is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN , CO_2H or SH ;

and wherein any available ring carbon position of formulae **III - XVII** can also be optionally replaced by $-N-$ when the valency and configuration of the formula allows, the point of attachment of formulae **III- XVII** to the A group defined above is represented by \blacklozenge ; and

wherein in formulae **XII, XIII**, m is selected from 2, 3 or 4, and

wherein in formulae **XII, XIII, XVI** and **XVII**, J is selected from CH or N;
and wherein in formulae **XIV** and **XV** n is selected from 0, 1 or 2;
and wherein in formulae **XVI** and **XVII** o is selected from 1 and 2.

The compound of formula II as claimed in claim 41 wherein the DNA targeting unit is selected from one of formulae **V, VI, VII, VIII, IX** or **X**.

The compound of formula II as claimed in claim 41 wherein D of the DNA targeting unit of Formulae **III - XI** is H or Me.

A compound of formula II as claimed in claim 41 selected from a compound; wherein X is $NH-$, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_2NH(CH_2)_2NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is $NH-$, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_3NH(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is 6-Me, Z is N, position 1-oxide, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$,
5 the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is H;

10 wherein X is NH-, Y is 6-Me, Z is N, position 1-oxide, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is H;

wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_2NMe(CH_2)_2NHCO-$, the DNA targeting unit represents formula IX and D is Me; and

15 wherein X is NH-, Y is H, Z is N, position 1-oxide, A is $-(CH_2)_3NMe(CH_2)_3NHCO-$, the DNA targeting unit represents formula IX and D is Me.

45 A method of treating a subject in need of cancer therapy, said method
20 comprising the steps of administering to said subject a cytotoxic effective amount of a compound of Formula II as defined in claim 34 to the tumour cells in said subject.

46 The method according to claim 45 wherein the tumour cells are in a hypoxic environment.

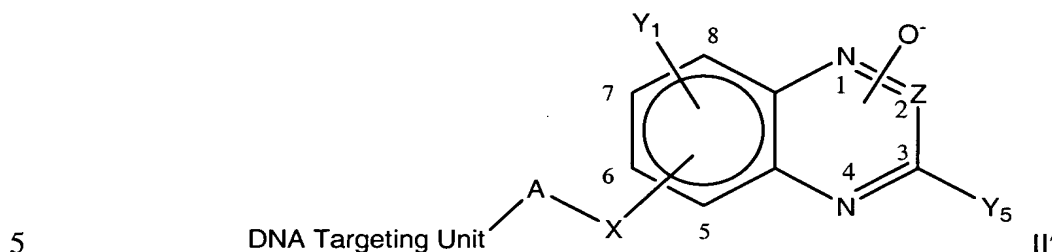
25 47 The method according to claim 45 which includes the further step of administering the compound of Formula II in combination with one or more other chemotherapeutic agents or treatments, including radiotherapy, either simultaneously, or sequentially, depending on the cancer therapy.

30 48 The method according to claim 45 radiotherapy is administered to the tumour cells before, during or after the administration of the compound of Formula II.

49 The method according to claim 47 wherein the chemotherapeutic agents are
35 selected from Cisplatin or other platinum-based derivatives, Temozolomide or other DNA methylating agents, cyclophosphamide or other DNA alkylating agents,

doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

50 A compound of Formula II',



wherein

Z is selected from N or C-CN, and when Z represents N, the N-oxide moiety occupies one of the 1-, 2-, or 4-positions; and when Z represents C-CN, the N-oxide moiety occupies one of the 1-, or 4-positions;

10

Y₁ represents at one or more of the available carbons 5-8 on the benzo ring the following groups:

halo, H, R, OH, OR, NO₂, NH₂, NHR, NR₂, SH, SR, SO₂R, CF₃, CN, CO₂H, CO₂R, CHO, COR, CONH₂, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

15

Y₅ is selected from the following groups halo, H, R, OR, NH₂, NHR, NR₂, SO₂R, CF₃, CN, CO₂H, CO₂R, CHO, COR, CONH₂, CONHR or CONRR, cyclic alkylamino, imidazolyl, alkylpiperazinyl, morpholino;

20

wherein each R of groups Y₁ and Y₅ is independently selected from an optionally substituted C₁₋₆ alicyclic or an optionally substituted C₃₋₆ cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR¹, NO₂, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂, CONHR¹, CONR¹R¹;

25

R can represent an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR¹, NH₂, NHR¹, NR¹R¹, SH, SR¹, imidazolyl, R¹-piperazinyl, morpholino, SO₂R¹, CF₃, CN, CO₂H, CO₂R¹, CHO, COR¹, CONH₂,

30

CONHR¹, CONR¹R¹, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R¹ is independently selected from an optionally substituted

C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional

5 substituents are each independently selected from OH, OR, NH₂, NHR², NR²₂ or N(OH)R² wherein each R² is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH, and

wherein X represents NH, NMe, CH₂, S, SO, SO₂, CONH, NHCO, CO, CO₂, or O;

10

A represents an optionally substituted C₁₋₁₂ alkyl group wherein the optional substituents are each independently selected from OH, OR³, NH₂, NHR³, NR³₂ or N(OH)R³ wherein each R³ is independently selected from C₁₋₄ alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and wherein the optionally substituted C₂₋₁₂ alkyl chain can be optionally

15 interrupted by one or more heteroatom containing linkage moieties selected from O, NH, NR⁴, CONH, CONR⁴, NHCO, NR⁴CO, where each R⁴ is independently selected from an optionally substituted C₁₋₄ alkyl or an optionally substituted C₂₋₄ alkenyl group and wherein the optional R⁴ substituents are each independently selected from OH, OR, NH₂, NHR⁵, NR⁵₂ or N(OH)R⁵ wherein each R⁵ is independently selected from C₁₋₄
20 alkyl, C₂₋₄ alkenyl, OH, NO₂, NH₂, CF₃, CN, CO₂H or SH; and

wherein the DNA-targeting unit is any moiety of a molecular weight below 700 Daltons that has an association constant (K) for binding to double-stranded random-sequence DNA of >10³ M⁻¹ at an ionic strength of 0.01 M at 20 °C,

25

or a pharmacologically acceptable salt thereof.

51 A compound of Formula II' as claimed in claim 50 wherein Z is N.

30 52 A compound of Formula II' as claimed in claim 50 wherein X is O or CH₂.

53 A compound of Formula II' as claimed in claim 50 wherein the N-oxide is at the 1-position.

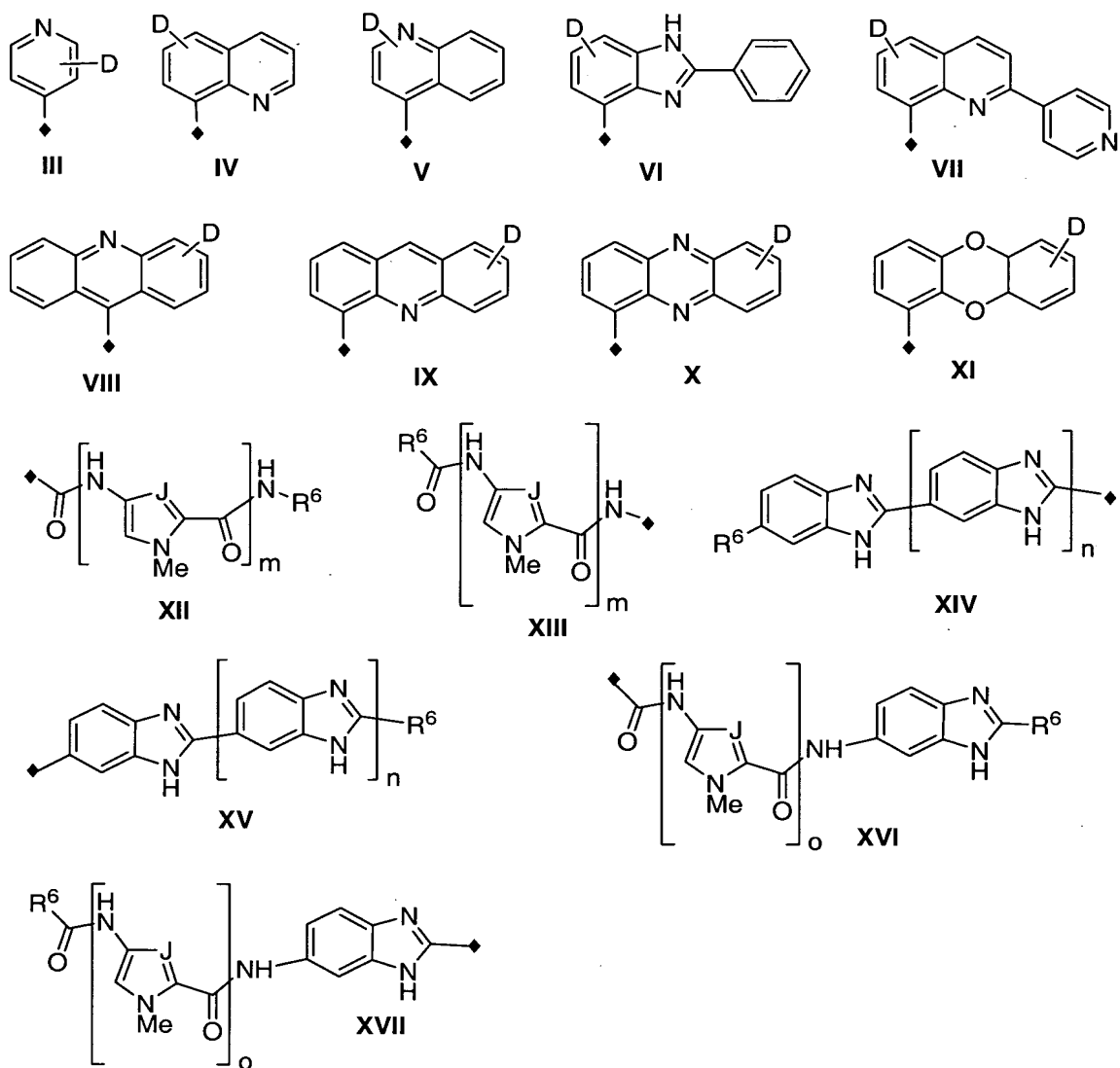
35 54 A compound of Formula II' as claimed in claim 50 wherein Y₁ represents H.

55 A compound of Formula II' as claimed in claim 50 wherein Y₅ represents NHR.

56 A compound of Formula II as claimed in claim 50 wherein A is selected from $-(CH_2)_6NH-$, $-(CH_2)_3NH(CH_2)_3NHCO-$, $-(CH_2)_3NMe(CH_2)_3NHCO-$, $-(CH_2)_3NH-$, $-(CH_2)_2NH(CH_2)_2NHCO-$ or $-(CH_2)_2NMe(CH_2)_2NHCO-$.

5

57 A compound of Formula II as claimed in claim 50 wherein the DNA-targeting unit is selected from one of formulae **III- XVII**,



wherein in structures **XII - XVII** R^6 is independently selected from an optionally substituted C_{1-6} alicyclic or an optionally substituted C_{3-6} cyclic alkyl group, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 , NO_2 , NH_2 , NHR^7 , NR^7R^7 , SR^7 , imidazolyl, R^7 -piperazinyl, morpholino, SO_2R^7 , CF_3 , CN, CO_2H , CO_2R^7 , CHO, COR^7 , $CONH_2$, $CONHR^7$, $CONR^7R^7$;

10

R^6 represents an optionally substituted aryl or an optionally substituted heteroaryl group having up to 12 carbon atoms, and wherein the optional substituents are each independently selected from; halo, OH, OR^7 , NH_2 , NHR^7 , NR^7R^7 , SH, SR^7 , imidazolyl, R^7 -piperazinyl, morpholino, SO_2R^7 , CF_3 , CN, CO_2H , CO_2R^7 , CHO, COR^7 ,
 5 $CONH_2$, $CONHR^7$, $CONR^7R^7$, and each heteroaryl group contains one or more heteroatoms in its ring system which are each independently selected from O, N or S;

wherein each R^7 is independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^8 , NH_2 , NHR^8 , NR^8_2 or
 10 $N(OH)R^{98}$ wherein each R^8 is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN, CO_2H or SH;

D represents up to four of the following groups as substituents at any available ring carbon position; H, R^9 , hydroxy, alkoxy, halogen, NO_2 , NH_2 , NHR^9 , NR^9_2 , SH, SR^9 , SO_2R^9 , CF_3 , CN, CO_2H , CO_2R^9 , CHO, COR^9 , $CONH_2$, $CONHR^9$ or $CONR^9R^9$, cyclic
 15 alkylamino, imidazolyl, alkylpiperazinyl, morpholino, wherein each R^9 independently selected from an optionally substituted C_{1-4} alkyl or an optionally substituted C_{2-4} alkenyl group and wherein the optional substituents are each independently selected from OH, OR^{10} , NH_2 , NHR^{10} , NR^{10}_2 or $N(OH)R^{10}$ wherein each R^{10} is independently selected from C_{1-4} alkyl, C_{2-4} alkenyl, OH, NO_2 , NH_2 , CF_3 , CN, CO_2H or SH;

20 and wherein any available ring carbon position of formulae **III- XVII** can be optionally replaced by -N- when the valency and configuration of the formula allows, the point of attachment of formulae **III- XVII** to the A group defined above is represented by \blacklozenge ; and wherein in formulae **XII** and **XIII**, m is selected from 2, 3 or 4,
 25 and wherein in formulae **XII**, **XIII**, **XVI** or **XVII** J is selected from CH or N; and wherein in formulae **XIV** and **XV** n is selected from 0, 1 or 2, and wherein in formulae **XVI** and **XVII** o is selected from 1 or 2.

58 A compound of Formula II' as claimed in claim 57 wherein the DNA targeting
 30 unit is selected from one of formulae IV – X.

59 A compound of formula II' as claimed in claim 57 wherein D of the DNA targeting unit of Formulae III – XI is H or Me.

35 60 A compound of formula II' as claimed in claim 57 selected from a compound;

wherein X is CH₂-, Y₁ is H, Y₅ is NHCH₂CH₂OMe, Z is -N-, A is -
(CH₂)₂NMe(CH₂)₂NHCO-, the DNA targeting unit represents formula IX and D is H;

wherein X is CH₂-, Y₁ is H, Y₅ is NHCH₂CH₂OMe, Z is -N-, A is-
5 (CH₂)₂NH(CH₂)₃NHCO-, the DNA targeting unit represents formula IX and D is H;

wherein X is CH₂-, Y₁ is H, Y₅ is NHCH₂CH₂OMe, Z is -N-, A is -
(CH₂)₂NMe(CH₂)₂NHCO-, the DNA targeting unit represents formula IX and D is Me;

10 wherein X is CH₂-, Y₁ is H, Y₅ is NHCH₂CH₂OMe, Z is -N-, A is -
(CH₂)₂NMe(CH₂)₃NHCO-, the DNA targeting unit represents formula IX and D is Me;

wherein X is CH₂-, Y₁ is H, Y₅ is NHCH₂CH₂OMe, Z is -N-, A is-
(CH₂)₂NMe(CH₂)₂NHCO-, the DNA targeting unit represents formula X and D is Me;
15 and

wherein X is CH₂-, Y₁ is H, Y₅ is NHCH₂CH₂OMe, Z is -N-, A is-
(CH₂)₂NH(CH₂)₃NHCO-, the DNA targeting unit represents formula X and D is Me.

20 61 A method of treating a subject in need of cancer therapy, said method
comprising the steps of administering to said subject a cytotoxic effective amount of a
compound of Formula II' as defined in claim 50 to the tumour cells in said subject.

62 The method according to claim 61 wherein the tumour cells are in a hypoxic
25 environment.

63 The method according to claim 61 which includes the further step of
administering the compound of Formula II' in combination with one or more other
chemotherapeutic agents or treatments, including radiotherapy, either simultaneously,
30 or sequentially, depending on the cancer therapy required.

64 The method according to claim 63 wherein radiotherapy is administered to the
tumour cells before, during or after the administration of the compound of Formula II'.

35 65 The method according to claim 63 wherein the chemotherapeutic agents are
selected from Cisplatin or other platinum-based derivatives, Temozolomide or other
DNA methylating agents, cyclophosphamide or other DNA alkylating agents,

doxorubicin, mitoxandrone, camptothecin or other topoisomerase inhibitors, methotrexate, gemcitabine or other antimetabolites.

66 A method of potentiating the cytotoxicity of an amount of a compound of
5 Formula B as defined in claim 1 or a composition including Formula B as defined in claim 1, which has been administered to a subject in need of cancer therapy, by administering to said subject a compound of Formula A as defined in claim 1 or a composition including Formula A as defined in claim 1.

10 67 The method as claimed in claim 66 which potentiates the hypoxic cytotoxicity of an amount of a compound of Formula B.

68 The method as claimed in claim 66 which includes the further step of
administering to said subject the compound of Formula A as defined in claim 1 or a
15 composition including Formula A as defined in claim 1 in combination with one or other chemotherapeutic agents or treatments defined above, including radiotherapy, either simultaneously, or sequentially depending on the cancer therapy required.

69 The method as claimed in claim 68 wherein radiotherapy is administered to
20 the subject, before, during or after the administration of said compound of Formula A or said composition including Formula A.

70 A method of potentiating the cytotoxicity of one or more chemotherapeutic
agents as defined above, administered to a subject, by further administering to said
25 subject a compound of Formula A as defined in claim 1 or a composition including Formula A as defined in claim 1.

71 The method as claimed in claim 68 which potentiates the hypoxic cytotoxicity
of the one or more chemotherapeutic agents.
30

72 The method as claimed in claim 71 which includes the further step of
administering radiotherapy to said subject, either simultaneously or sequentially
depending on the cancer therapy required.

35 73 The method as claimed in claim 72 wherein the step of administering radiotherapy to the subject, occurs before, during or after the administration of said compound of Formula A or said composition including Formula A.